Double Chromosomal Abnormalities in Live Birth Infants

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Abstract

Objectives: The aim of this study was to present rare cases with coexistence of double chromosomal abnormality involving chromosome 21 and to discuss different mechanisms of double anomaly in live births for better counseling.

Introduction: The coexistence of two chromosomal abnormalities in the same individual is relatively a rare phenomenon. Most of the previously reported cases of double abnormality were found in spontaneous abortions. Multiple chromosomal abnormality occurs as a consequence of a minimum of two errors during meiosis. The zygote carrying a double anomaly usually results from a double error in a single germ cell. However the coincidence of a single anomaly occurring in both gametes was also observed.

Material and Methods: In this study, we described nine live births with double chromosomal abnormality involving chromosome 21. Cytogenetic studies and fluorescence in situ hybridization (FISH) analysis were carried out for all infants and their parents. The first newborn had double trisomy involving chromosomes 21 and X in a female infant (karyotype 48,XXX,+21). Second and third cases had both trisomy 21 and trisomy 18 (karyotype 48,XX,+21,+18) the fourth case had apparent monosomy 21 and trisomy 18 (karyotype 46XX,-21,+18). Cases 5-9 had trisomy 21 associated with deletion or translocation. In all cases the double chromosomal abnormality is de novo except in cases 1 and 6.

Conclusion: We concluded that genetic counseling in such cases is difficult. Neither satisfactory data concerning the clinical outcome of the double chromosomal anomaly in live infants nor any information concerning the recurrence risk for their parents. However, we recommend the study of different tissues to parents of children with de novo double chromosomal anomaly.

Key Words: Double chromosomal abnormalities – Live birth infants.

Introduction

FULL aneuploidy is presumed in the great majority to be the result of meiotic nondisjunction. A diminished degree of meiotic recombination is typically observed and this has led Hassold and Sherman [1] to propose a two-hit sequence, the first hit being a less well-tethered bivalent at meiosis I and the second hit being a consequential aberrant distribution at meiotic metaphase. Meiotic nondisjunction can happen at any maternal age, but it is more frequent in older mothers. Alternatively, an abnormality has arisen in a premeiotic gametocyte, with the parent thus having a "wedge" of gonad that carries the abnormality (gonadal mosaicism). Such a parent would, of course, have an increased risk for only the one karyotype defect. Finally, a small fraction of apparent full aneuploidy may be due to early mitotic nondisjunction in an initially 46, normal conceptus with loss of the normal cell line or restriction to extra embryonic tissue of the normal cell line [2].

The coexistence of two chromosomal abnormalities in the same individual is relatively a rare phenomenon. Multiple aneuploidy (occurs when all or part of one or more chromosome is added or deleted), it occurs as a consequence of a minimum of two errors during meiosis. The zygote carrying a double aneuploidy usually results from a double nondisjunction in a single germ cell however the coincidence of a single aneuploidy occurring in both gametes was also observed [3,4]. Double aneuploidy is not uncommon outcome of pregnancy being more reported in abortions, stillbirths and prenatal diagnosis, but rarer in live born [5]. Two different types of abnormality such as klinefelter plus Prader-Willi syndrome might reflect two unrelated abnormal events [6]. Gardner and Sutherland [7] postulated that the probability of such two abnormal karyotype coinciding might be a very small (one in thirty millions). What makes the survivors different from the aborters? Could it be that they have tissue specific mosaicism with the additional normal cell line supporting survival? It has been suggested that the presence of an euploid placenta could create an in utero environment that
will maintain these double trisomies to reach birth [8].

The aim of this study is:

(1) To present rare cases of possible coexistence of double chromosomal abnormality involving chromosome 21 and to discuss different mechanisms of the double anomaly in live births for better counseling.

Case Reports

The studied cases were seven females and two male infants, referred from Genetics Clinic at El-Galaa Teaching Hospital and Human Genetics Clinic at National Research Centre, Cairo, Egypt.

The first female neonate was two days old, she had craniofacial anomalies as upward slanting palpebral fissure, epicanthic folds, flat nasal bridge, small mouth and thick lips.

She had a single palmer crease with wide space between the first and second toes, with hypotonia. Chest X-ray revealed VSD (Ventral septal defect). Down syndrome was highly suspected. Her karyotype showed nonmosaic cell line of 48, XXX, +21. She did not survive long after diagnosis. Her family pedigree showed that she was the second daughter after a two years older apparent healthy sister.

The non relative parents were in the twenties. There were no similar conditions among their families. Their karyotype showed that the father’s had normal male karyotype.

The mother was mosaic for 45, X (10%)/46, XX (80%)/47, XXX (10%).

Our second neonate was referred to our cytogenetic laboratory with craniofacial dysmorphism including prominent occiput, narrow bifrontal diameter, short palpebral fissure, small mouth, narrow palate, left low set ear and micrognathia rocker bottom feet. She was delivered by Caesarian section at 36 weeks of gestational age, she was of low birth weight and respiratory distressed, with probable cardiac anomaly. She died at the age of 7 days. Her family pedigree showed that she was the first child, the parents were cousins, with ages around twenties. The child’s karyotype was mosaic of: 47, XX, +21 (80%), 48, XX, +21, +18 (20%).

The fourth female was seven days old. She was the first child to a consanguineous marriage of a couple in the early twenties. The neonate had hypotelorism, cleft lip and palate cryptophthalmia and clitromegaly. Her brain CT revealed semi lobar holoprosencephaly, partial agenesis of corpus callosum and cortical dysplasia. The parental lymphocyte karyotype was normal. The lymphocyte of the proband was 46, XX, -21, +18. FISH results showed that the neonate had partial proximal deletion in chromosome 21 with partial trisomy in chromosome 18 (q). The patient died at age of 15 days.

Case 5 is a 9 month male who had Down syndrome features and had double Robertsonian translocation, 45, XY, t(13;14), (t21;21).

Cases 6-8 have trisomy 21 associated with translocation 47, XY, +21, t(5;21). 47, XX, +21, t(8;10). 47, XX, +21; t(2;12).

Case 9 had trisomy 21 and deletion 5, 47, XX+21, del (5) (p15) and died after 3 days.

Cytogenetic studies:

Chromosomal analysis was performed on phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes, then GTG-banding technique [9]. Metaphases were analyzed under the microscope and nomenclatured according to ISCN [10], (for the children and their parents). FISH was done for confirmation when needed [11], using whole chromosome paint, locus specific identifier and centromeric probes.

Results

Cases 1-3 had double aneuploidy involving chromosome 21 with X or 18 (Figs. 1,2).

Case 4 had trisomy 18q and proximal monosomy 21q (Fig. 3). 46,XX,ish der (18) (t18;21) (p11.2;q11.2) dup (18) (q11.2.q23) (wcp18++, lsi21 q22++, cen 18 +++, 21 qtel ++), (Figs. 4-6).

Case 5 had double Robertsonian translocation 45, XY, t(13;14), t(21;21) (Fig. 7).

Case 6 had 47, +21, t(5;21) (Fig. 8).

Case 7 had 46, XX, +21, t(8;10) (Fig. 9), case 8 had 46, XX, +21, t(2;12).

Case 9 had 46, XX, +21, del (5) (p15).
Fig. (1): FISH using whole chromosome paint for X (green) and 21 (red) showing three signals for X and 21 (case 1).

Fig. (2): Female karyotype showing trisomy of both 18 and 21 (case 2).

Fig. (3): Female karyotype showing apparently 46, XX, -21, +18 (case 4).

Fig. (4): FISH using LSI (21q22) green and WCP 18 red showing 3 signals for 18 and two signals of 21 (case 4).

Fig. (5): FISH using alpha satellite probe for centromere 18 showing 3 signals (case 4).

Fig. (6): LSI for 21 q telomere showing two signals (case 4).
Fig. (7): Male karyotype showing 45, XY, t(13;14), t(21;21), (case 5).

Fig. (8): Male karyotype showing 47, XY, +21, t(5;21).

Fig. (9): Female karyotype showing 47, XX, +21, t(8;10).

**Discussion**

Our first female case was having a karyotype of triple X and trisomy 21, born to a mother carrying mosaic cell line of X/XX or X/XX/XXX. Sybert [12] recorded that mothers with X/XX or X/XX/XXX mosaicism had 44 live births of which 5 expressed sex chromosome aneuploid and 2 cases expressed trisomy 21. Li, et al. [13] documented similar cases to be rare. Earlier study (Reddy, 1977) [14] reported that double aneuploid involving autosome 21 and sexual chromosome may reach 9.9% in live born who had double trisomy. Bravo, et al., 1994 [15] reported a similar combination in the fetus of a young mother from amniocentesis at 17.5 weeks of gestation following a serum analyte screen, confirmed by ultrasound and FISH of amniocytes. Proceeding in further molecular study, aneuploid was due to non disjunction in meiosis II. Other authors recorded trisomy 21 associated with klinefelter syndrome [16,17].

It is postulated that sex cells contain a control station for monitoring the mechanism that ensures that the correct numbers of chromosomes are distributed during cell division. Scientist added that there is an alternative distribution mechanism in female sex cells that cause chromosome disorders. Aberrant chromosomes orientate themselves like normal chromosomes and this ability to adopt double identities protects them from detection by the control centre [18].

The incidence of Down syndrome among the offspring of young mothers has led to hypothesis of the involvement of certain autosomal recessive genes that might be involved in the genetic control of non-disjunction meiosis [19]. Recent studies compiled paternal age analysis as origin in trisomy 21 [1].

The second case in our study was clinically referred for confirmation of Edward Syndrome (Trisomy 18). Her karyotype was mosaic of 47, XX+18 (80%)/48, XX+18+21 (20%). Meanwhile the third case was also a female, who was referred for confirmation of trisomy 21. Her lymphocyte karyotype was mosaic of 47, XX+21 (80%)/48, XX+18+21 (20%). There was no clear association between the limited mosaicism seen and severity of the phenotype in the second and third case. Though the two cases were mosaic, one was consistent with Edward’s syndrome; the other showed Edward (microcephaly)-Down syndrome features. Bravo et al. [15] postulated that multiple aneuploidy are more likely to arise by related errors than independent errors in different cell division or different gametes. It has been suggested that the presence of an euploid placenta could create an in utero environment that will maintain these double trisomies to reach birth [8].
Two similar cases were reported one by Gross and Schwarrtiz, 1997 [20], the other by Sadika in 1999 [21]. Though their cases were non mosaics, the first was consistent with Down syndrome phenotype, while the second was consistent with Edward syndrome.

Thus mosaicism could not be the only explanation expressing phenotype. The demonstration on regulatory mechanism controlling phenotype/karyotype needs more investigation.

Acrocentic chromosomes appear frequently in multiple cases with a particular double trisomy and also partner a wide range of chromosomes [14]. Several combinations do appear more frequently than others, the author reported that chromosomes 18 and 21 combination might reach 1.7% in liveborns who had double aneuploidy. This would suggest that non-viability of conceptions carrying a double trisomy would depend on which chromosomes are involved in the aneuploidy, either because of a more or less severe gene dosage imbalance or due to epigenetic factors such as genomic imprinting (differential expression of genes depending on parental origin).

Recent screening prenatal programs and the notion of aborting the unwanted outcome of pregnancies might be the cause of decreased the incidence in this decade.

The mean gestational age has been described to be significantly lower for double trisomy cases than that reported for single trisomy ones [14]. However, some cases of double trisomes involving chromosomes 8, 13, 18, 21, X and Y have been observed in liveborns, suggesting that lethality of the abnormality depends on which chromosomes are involved in the aneuploidy.

However our two cases were delivered at 36 weeks of gestation which is considered as full term neonate. Sequential non disjunction at both meiotic divisions could lead to tetrasomy, Chen et al. [20] described 48, XXX, +18 resulted from non disjunction of X and 18 in maternal meiosis II. Simultaneous parental non disjunction, with both gametes being disomic is rare but not unknown.

The fourth case was apparently by conventional lymphocyte karyotype non mosaic of 46, XX, -21, +18. FISH results revealed the case to be 46, XX, der (18) t(18;21) (p1 1.2;q1 1.2) dup (18) (q1 1.2,q23) del (21) (q11). Rare cases are documented on monosomy 21, Joosten, et al., 1997 [23] and Ma, et al., 2001 [24]. Holoprosencephaly (semi lobar type) of unknown definite causes, has been associated with several abnormalities involving the autosome and the sex chromosomes, including monosomy 21 [25,26]. The clinical features in our case was mostly described in cases with trisomy 18 and proximal deletion of chromosome 21. Some authors providing the term proximal monosomy 21q syndrome [27,28].

Studies from literature on aneuploid cells are recently registered after in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) centers (ICSI). Borrello, et al. [29], reported an increase in de-novo chromosomal abnormalities and higher frequency of 7 transmitted chromosomal aberrations were found in a large cohort of 1082 conceptions through prenatal genetic diagnosis from a single IVF centre. While Ma, et al. [24], added that though the issue of ICSI as powerful procedure in fertilization, there is a debate about genetic implications in the increased rate of chromosomal abnormalities in the resulting pregnancies.

The karyotype in case 5 [45, XY, t(13;14), t(21;21)] may suggest that the first event was t(21;21), occurred in parental meiotic division and as there is no normal copy of either 13 or 14, we postulated that the second error t(13;14) happened in early zygotic division.

Case 6 had 47, XY, +21,t(5;21), The mother had balanced translocation, Braddock et al. [30] reported a case with a tertiary trisomy due to a reciprocal translocation of chromosomes 5 and 21. Such families with reciprocal translocation needs genetic counseling and prenatal diagnosis to discover any malsegregation. Case 9 had features more sever than those with trisomy 21, the occurrence of such two unrelated abnormalities is very rare and may account one in several millions [7].

Registration of all cases with double anomalies is very important some authors consider it very rare and others have suggested that double anomaly might be more common than the product of their individual frequencies [31].

We thus conclude that cytogenetic and molecular cytogenetic (FISH) studies are highly recommended, in cases with typical or atypical syndromes. The follow-up and registration, is worthy to enable the studying of the impact of double abnormalities in live births. The recommendation of karyotyping multiple parental tissues as well as molecular cytogenetic studies might be equally important in counseling families with de novo cases, as well as in families with recurrent affected sibs.
References


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